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Imaging predictors of post-stroke depression: Methodological factors in voxel based analysis

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Objective: The purpose of this study was to explore the relationship between lesion location and post-stroke depression using statistical parametric mapping.

Methods: First episode stroke patients were assessed within 12 days and at one month post-stroke. Patients with an a-priori defined cut-off score of 11 on the Hospital Anxiety and Depression Scale (HADS) at follow-up were further assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.) to confirm a clinical diagnosis of major or minor depression in accordance with DSM-IV inclusion criteria. Participants were included if they were aged 18-85 years, proficient in English and eligible for magnetic resonance imaging (MRI). Patients were excluded if they had a compounding diagnosis such as major depressive disorder at the time of admission, a neurodegenerative disease, epilepsy, or an imminently life-threatening comorbid illness), subarachnoid or subdural stroke, a second episode of stroke before follow-up, and/or a serious impairment of consciousness or language. Infarcts observed on MRI scans were manually segmented into binary images, linearly registered into a common stereotaxic coordinate space. Using statistical parametric mapping, we compared infarct patterns in stroke patients with and without depression.

Results: Twenty-seven percent (15/55 patients) met criteria for depression at follow-up. Mean infarct volume was 19 ± 53 ml and National Institute of Health Stroke Scale (NIHSS) at Time 1 (within 12 days of stroke) was 4 ± 4, indicating a sample of mild strokes. No voxels or clusters were significant after a multiple comparison correction was applied ($p > 0.05$). Examination of infarct maps showed that there was minimal overlap of infarct location between patients, thus invalidating the voxel comparison analysis.

Conclusions: This study provided inconclusive evidence for the association between infarcts in a specific region and post-stroke depression.

Strengths and limitations of this study:

- This prospective study is the first lesion location study in post-stroke depression to use voxel based analysis. It demonstrates the challenges in using this method of analysis for this cohort and discusses ways of addressing these issues in future research.

- Limitations include that the study provided inconclusive evidence for the association between infarcts in a specific region and post-stroke depression. Additionally, infarct volumes were small, precluding further analysis and suggested that we had unintentionally recruited patients with mild strokes.

Introduction

Post-stroke depression, i.e., affective disorders following stroke, has been described to affect more than 30% of patients with stroke. It has been associated with increased mortality [1-3], cognitive impairment [1], greater functional impairments [4], poorer rehabilitation outcomes [2,3] and reduced health related quality of life [5]. An understanding of patients at risk of post-stroke depression would help guide preventive interventions. The postulate for a neurobiological basis of post-stroke depression was based on observed behavioural changes in rats following focal cortical lesions, and concurrent change in catecholamine levels [6]. Human studies later suggested that depression was more likely after stroke affecting the left hemisphere or frontal lobe [7]. This idea of lesion location impacting on post-stroke depression is an attractive one given the finding of lesion location causing neurological deficit post-stroke [8]. However, the role of lesion location in post-stroke depression remains a point of controversy due to conflicting results [9-11].

Modern studies of lesion location use brain imaging analysis tools to characterise ensembles of voxels representing the network of regions involved [8]. However, earlier studies and those assessed in review papers focussed on coarse analyses differentiating left from right hemisphere stroke or anterior versus posterior lesion locations, and their resultant relationship with depression. In light of the improved sensitivity to regional abnormalities afforded by voxel based analysis, the aim of this study was to examine the role of lesion location in post-stroke depression. In the process of performing this analysis we encountered several issues with voxel based analysis for depression in stroke patients.

Materials & methods

Participants

Participants were patients who presented to Monash Medical Centre and Dandenong Hospital with a first cerebral infarction or haemorrhage (*N*=71) in Melbourne, Australia between May 2009 and September 2010. Participants were included if they were aged 18-85 years, proficient in English (i.e., capable of completing the assessment materials), and eligible for magnetic resonance imaging (MRI). Participants were excluded if they had a compounding diagnosis (major depressive disorder at the time of admission, a neurodegenerative disease, epilepsy, or an imminently life-threatening comorbid illness), had a subarachnoid or subdural haemhorrage, if a second episode of stroke occurred before follow-up, and/or they were deemed incapable of participation due to incapacity (serious impairment of consciousness or language). The language component of the National Institute of Health Stroke Scale (NIHSS) and the Multilingual Aphasia Examination's (MAE) Token Test (Form A), a 22-item test of oral language comprehension [12], were used to complement clinical judgment in cases with language disturbance. Ethics approval was received from Southern Health and Monash University Human Research Ethics Committees. All participants provided written informed consent.

Test administration and procedure

MRI scans were performed as part of clinical care. Cognitive functioning, stroke severity, physical disability and handicap and demographic information were acquired at Time 1 (typically within 10 days of stroke). Depression was assessed at Time 2 (one month since stroke).

Measures

Cognitive functioning was assessed using the ACE-R [13]. The NIHSS was used to determine stroke severity [14]. The Modified Rankin Scale (MRS) was used to measure both physical disability and handicap [15,16]. The scale ranges from 0-6 from "No symptoms at all", to "Death". The Hospital Anxiety and Depression Scale (HADS) has been used routinely within stroke to screen for symptoms of depression [17]. Those with a cut-off score of 11 on the HADS were further assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.), a semi-structured clinical interview, to confirm a clinical diagnosis of major or minor depression in accordance with DSM-IV inclusion criteria [18,19]. The M.I.N.I. was administered by a provisional psychologist. This procedure was used to optimise sensitivity, as a cut-off score of 11 on the HADS has been found to have a sensitivity of 86.8 for detecting major and minor depression, and a specificity of 69.9 [20]. The M.I.N.I displays high validity and reliability in relation to the Structured Clinical Interview for DSM, Patient Edition (SCID-P), and the Composite International Diagnostic Interview (CIDI). The M.I.N.I. can be administered in a shorter period of time than the aforementioned tools [18].

Image acquisition

MRI scans were performed on a 1.5 Tesla superconducting imaging system (General Electric Medical Systems, Milwaukee, WI) with echo-planar imaging capabilities. T2 images were acquired using thickness 6mm/1.7 mm, matrix 256 x 256, and TR/TE/ETL 2 000/102/12. Diffusion-weighted imaging (DWI) was performed with 6/1.7 mm thickness, matrix 128 x 256, field of view 230 mm, and TR/TE 10,000/102. Diffusion gradient values of 0 s/mm^2 and 1,000 s/mm^2 were applied in 3 directions.

Isotropic ADC maps were calculated on a voxel by voxel basis. The 3-D time of flight MRA was performed using TR/TE 38/6.9, 25^0 flip angle, thickness 1.4 mm, slab thickness 60 mm, matrix 256 X 224, field of view 180 mm.

Registration and segmentation

Alignment of corresponding anatomical structures in images (prior to segmentation) from different subjects was achieved by linear registration to a standard brain template comprising images from 152 subjects placed into the stereotaxic coordinate space (MNI template available at http://www.bic.mni.mcgill.ca/software/). Infarcts were manually segmented on the native T_2-weighted images using interactive *Display,* mouse driven software and standardised intensity windows. The transformation matrix was used to convert native segmented images into standard stereotaxic space.

t statistics

A parametric voxel based analysis (SPM; Wellcome Trust Centre for Neuroimaging, London, England) was used to produce statistical parametric maps. Images were spatially smoothed with a Gaussian kernel of 12 mm. This analysis used the two-sample *t* test in SPM5 to compare the distribution of the means of infarcts of patients with and without depression. A spatial mask of the sum of all infarcted regions in this sample (based on images before they were spatially smoothed) was applied so that the voxel analysis was constrained to this area. A false discovery rate (FDR) was used to correct for multiple comparisons, as the *t* statistic is applied to many voxels within the images. The FDR controls the expected proportion of false-positives among the voxels that have exceeded a certain threshold on the raw *t* statistics map [21]. The FDR was set at 0.05 so that among the significant voxels above the *t* threshold, 5%

would be considered false-positive. To assess the validity of the *t*-statistics images, an average map of the infarcts was generated. This process allows determination if the analysis contains infarcts which cover most of the brain. Previous investigators have been criticised for performing studies on infarcts belonging to a restricted arterial territory and hence in this study we include infarcts from any arterial territory [22].

Volume and overlap of infarcts

The volume of each infarct was calculated using a voxel counting algorithm. The overlap of infarcts amongst patients was manually examined to aid interpretation of results. The maximum overlap of regions of infarction between (i) all patients was seven; (ii) depressed patients was two; and (iii) patients without depression was seven (see Figures 1 and 2). A mask was used to determine the volume of infarcts in the anterior and posterior regions of the left and right hemispheres.

Results

Clinical Characteristics

Of the 71 participants, 55 (31 males) completed all aspects of the study including an MRI scan. Ten of the 71 patients withdrew or were lost to follow-up and one was excluded following a second episode of stroke. The clinical characteristics of participants are summarised in Table 1. The mean age was 62.9 years (*SD* = 13.6). Eighty percent (*n* = 44) of patients had ischaemic strokes. The mean NIHSS at Time 1 was 4 ± 4, representing minor strokes. Acute and follow-up assessments were administered within an average of 6 ± 3 days (range 1-12) and 33 ± 8 (range 25-74) days of stroke respectively. MRI scans were performed within an average of 20.8 ± 23.7 days of stroke (0-85 days). Overall, 27.3% of patients experienced depression (*n* = 15), either major (*n* = 9; 16.4%), or minor (*n* = 6; 10.9%). The mean total HADS score was 10 ± 7 (0-29).

Table 1. Clinical characteristics of participants, (N = 55)

Characteristic	
Mean age ± *SD* (yrs)	63 (*14*)
Range	29-85
Sex, *n* (%)	
Male	31 (56)
Female	24 (44)
Type of stroke[1], *n* (%)	
Ischaemic	47 (86)
Haemorrhagic	6 (11)
Laterality of stroke[2], *n* (%)	
Left	29 (53)
Right	20 (36)
Bilateral	5 (9)
Modified Rankin at Time 1[3], *n* (%)	
0-2 (no symptoms-slight disability)	31 (57)
3-5 (moderate-severe disability)	23 (43)
Mean NIHSS at Time 1 ± *SD*	4 ± 4
Range	0-21
Mean ACE-R at Time 1 ± *SD*	78 ± 16
Range	18-99
Mean infarct volume ± *SD* ml	19 ± 53
Range	0-350*
English first language, *n* (%)	40 (73)
Personal history of depression, *n* (%)	12 (22)
Family history of depression, *n* (%)	5 (9)
Antidepressants during study, *n* (%)	3 (6)
Depression at Time 2, *n* (%)	15 (27)

*0 volumes represent scans with no visible infarcts despite clinical diagnosis of stroke.
[1]Two cases of missing data; [2,3]One case of missing data.

Image analysis

The mean infarct volume was 19.4 ± 53.2 ml (0-349.8 ml). Stroke occurred in the left hemisphere in twenty nine (52.7%) patients, right hemisphere in 20 patients (36.4%). It was present in both hemispheres in 5 patients (9.1%). The mean volume of infarct in the left hemisphere was 6.2 ± 15.6 ml and the right hemisphere was 38.0 ± 83.2 ml (p = 0.001). The mean volume of infarct in the left anterior region was 4.8 ± 7.7 ml and the right anterior region was 46.9 ± 91.4 ml (p=0.06). The mean volume of infarct in the left posterior region was 16.2 ± 27.2 compared to 17.6 ± 19.8 ml for the

right posterior region (p>0.05). Modified Rankin Scale scores greater than 2 were associated with larger lesion volumes (p = 0.02) and there was a large and medium correlation respectively between NIHSS scores acutely and at one month and lesion volumes (p < 0.05).

The average map of infarcts is displayed in Figure 1 and showed that infarcts occurred predominantly around the internal capsule and striatocapsular region. Infarct extent was greater on the right. The infarct pattern of the depressed group versus the group without depression was significant at the uncorrected level (p < 0.01, see Figure 2). No voxels or clusters were significant after the FDR correction was applied (p > 0.05). Additionally, there was no relationship between left anterior strokes and depression (p > 0.05). Infarct location of stroke by group is displayed in Table 2.

Table 2. Frequency of depressed and non-depressed patients by infarct location identified on MRI scans.

Infarct location	Group	
	Depressed	Not depressed
Left hemisphere, *n* (%)	7 (13)	20 (36)
Left anterior, *n* (%)	4 (7)	13 (24)
Left posterior, *n* (%)	3 (5)	7 (13)
Right hemisphere, *n* (%)	5 (9)	15 (27)
Right anterior, *n* (%)	4 (7)	11 (20)
Right posterior, *n* (%)	1 (2)	3 (5)
Extended across the anterior and posterior cortex, *n* (%)	0	1 (2)
Bilateral, *n* (%)	1 (2)	2 (4)
No infarct on MRI scan	2 (4)	3 (5)

Note. 6 (11%) of infarct locations displayed above differ from values displayed in Table 1 which relate to hemispheric location documented in patients' medical records.

When potential confounders including sex, a history of depression, cognitive functioning and physical disability and handicap were analysed for inclusion in the image analysis, sex was the only variable significantly related to mood (p<0.0.5). When the infarct analysis was repeated with gender as a covariate, infarct location was not significantly related to depression after a FDR correction was applied (p>0.05). An independent samples t-test indicated no significant difference in lesion volume between groups with and without depression (p>0.05).

Discussion

Based on the results of this study, the contribution of lesion location to the aetiology of post-stroke depression remains inconclusive. In the planning of this study, we had followed the suggestions of previous investigators with regards to including stroke from all arterial territories but in doing so had unintentionally created challenges for ourselves [22]. This study highlights the challenge in conducting voxel based analysis for lesion location studies in post-stroke depression. These issues related primarily to the use of strict inclusion and exclusion criterion, principally, the exclusion of patients with severe dysphasia and those patients who were likely to require institutionalised care. This action posed major challenges for voxel based analysis which required the presence of regions which overlap with each other. Below we discus how these results compare with prior studies, the theoretical implications, the issues affecting our results and propose methods to overcome these shortcomings in future studies of post-stroke depression.

Literature review

The current findings differ from prior studies, many of which have proposed that lesions to the left frontal cortex and basal ganglia are related to the onset of post-stroke depression, and proximity of the lesion to the frontal pole is associated with severity of depression [7,23-27]. More recently, MRI studies have supplemented earlier CT studies, providing further support for a relationship between lesions to the basal ganglia and PSD [28]. Other studies, however, have reported no significant relationship between lesion location and depression, with inconsistent findings attributed to methodological differences including timing of assessment [23,29]. Prior studies have defined lesion location based on whether lesions fall within a particular a

priori defined region of the brain [7]. Hence, whilst the results were less precise than voxel based morphology, overlap of precise lesion location was not required. However, in the current study when the occurrence of depression was compared in patients with anterior and posterior strokes in left and right hemispheres, no relationship was found.

Methodological considerations

i. Image analysis

When analysing the findings of voxel based analysis, one is often drawn to the significant results. A more useful approach is to examine the average map of all infarcts (Figure 1) to ensure there are no regions without infarcts. In our case, the map showed a predilection of larger infarcts in the right hemisphere compared to the left. This visual analysis paralleled our finding with the infarct volume between the hemispheres. These findings preclude any further voxel based analysis.

ii. Inclusion and exclusion criterion

In our patients the infarct volumes were small as was the NIHSS score. This suggested that we had unintentionally recruited patients with mild strokes. This has occurred because of the concern that assessment of depression was unreliable in patients with severe dysphasia. The second problem occurred because patients with larger strokes had impaired alertness and awareness and were not able to provide informed consent; in this study we did not used carer consent as is often done in the initial stage of acute stroke trials. As was the case with our study, the results of prior works were likely biased due to the same pitfall of excluding patients with severe dysphasia.

iii. Sample size

One approach is to significantly increase the sample size to allow the chance of overlapping regions of infarct. However, a 3-fold increase in sample size would only result in an overlap of 6 scans. Hence, it is probable that the selection of 'minor' strokes is significantly contributing to this methodological issue. A larger sample size would not resolve this issue unless the inclusion and exclusion criteria are changed to prevent exclusion of aphasic and severe stroke patients.

Strategies for recruitment may include assessment of patients in the sub-acute rather than the acute phase of stroke (Time 1). This may allow for some degree of neurological recovery, especially among patients with severe strokes, to increase the chance of recruitment of these patients. Alternatively, a non-verbal assessment of depression could be administered, such as the observer-rated Stroke Aphasic Depression Quesionnaire-10 [30] or the Aphasia Depression Rating Scale [31], however, there is currently limited information regarding the psychometric properties of these tools which implies a validation study is necessary as a first step. Finally, restricting inclusion to patients with infarcts within an a priori defined anatomical region would increase overlap of infarcts, although this method has received criticism [32]. Restricting arterial territory has previously lead to adequate overlap and significant results using voxel based analyses [33].

Future directions

Despite the abovementioned challenges encountered with neuroimaging within this patient group, further research is warranted. A greater understanding of the lesion characteristics associated with post-stroke depression could lead to advances in

diagnosis, preventive interventions and treatment. Additionally, the high prevalence of depression found within this sample despite no particular significant lesion location related to depression points to the benefit of analysing networks of neural structures implicated in depression, rather than limiting the focus to the significance of lesions to one or two structures. This approach could involve an a priori hypothesis regarding lesions restricting particular neurochemical pathways and associated structures or an alternative type of analysis that explores the significance of neural networks to the outcome of interest, such as partial least squares regression. Voxel based analysis could therefore be used in future studies of comparable sample size if inclusion criteria was restricted to an a priori defined homogenous subgroup of patients. This would allow hypothesis testing of the role of particular anatomical locations in post-stroke depression such as the basal ganglia. However other potentially relevant infarct locations would not be detected using this approach. An alternative method of analysis such as partial least squares regression might therefore be more appropriate as this technique would allow the involvement of networks of neural structures to be explored (Phan et al., 2010). However, partial least squares regression also requires the presence of infarcts in regions which overlap across images and would therefore only be appropriate if a non-verbal measure of depression was used to allow for the inclusion of patients with more severe strokes. Preliminary investigations showed that neither voxel based analysis nor partial least squares regression were appropriate in this study due to the nature of the data.

Conclusions

In summary, the results of this study do not provide evidence that infarcts to a particular neuroanatomical region contributes to post-stroke depression, however,

results should be interpreted with caution due to methodological limitations. Future studies could overcome the methodological issues encountered during our study by assessing patients within the sub-acute rather than the acute post-stroke period, using an observer rated scale of depression rather than measures that require language comprehension abilities, or including patients with infarcts within an a priori defined anatomical region. Alternatively, an analysis of lesions to neurochemical networks implicated in depression could shed light on the debate.

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Contributorship

Sophia Gozzi designed the study, recruited patients, collected and analysed data, drafted and revised the paper. Thanh Phan assisted with the study design, monitored data collection, segmented the infarcts on the MRI scans, assisted with image analysis and critically reviewed the paper. Amanda Wood assisted with the study design, monitored data collection, assisted with image analysis and critically reviewed the paper. Jian Chen assisted with image analysis and critically reviewed the paper. Krishnarao Vaddadi assisted with the study design and critically reviewed the paper. Imogen Rehm, Kitty Wong and May Chong assisted with patient recruitment and data collection.

Competing interests

None

Disclosure

None

Legends to figures

Figure 1: Average map of infarcts for all patients in stereotaxic coordinate space from z = -20 to z = 20 (from left to right).

Figure 2: Average map of infarcts for the depressed (blue) and not depressed (yellow) groups in stereotaxic coordinate space from z = -20 to z = 20 (from left to right).

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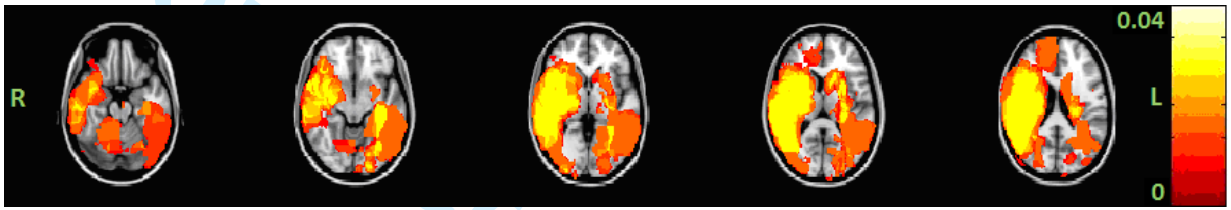

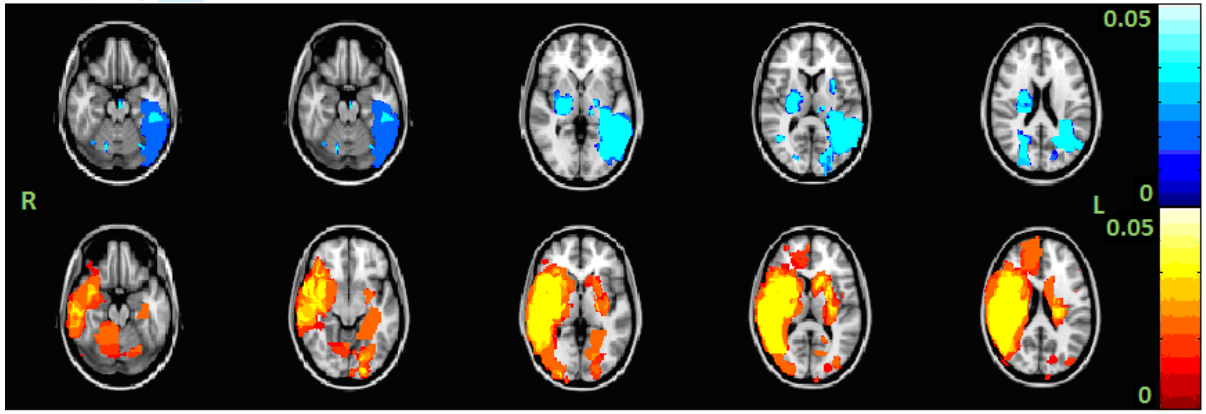

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Objective: The purpose of this study was to explore the relationship between lesion location and post-stroke depression using statistical parametric mapping.

Methods: First episode stroke patients were assessed within 12 days and at one month post-stroke. Patients with an a-priori defined cut-off score of 11 on the Hospital Anxiety and Depression Scale (HADS) at follow-up were further assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.) to confirm a clinical diagnosis of major or minor depression in accordance with DSM-IV inclusion criteria. Participants were included if they were aged 18-85 years, proficient in English and eligible for magnetic resonance imaging (MRI). Patients were excluded if they had a confounding diagnosis such as major depressive disorder at the time of admission, a neurodegenerative disease, epilepsy, or an imminently life-threatening comorbid illness), subarachnoid or subdural stroke, a second episode of stroke before follow-up, and/or a serious impairment of consciousness or language. Infarcts observed on MRI scans were manually segmented into binary images, linearly registered into a common stereotaxic coordinate space. Using statistical parametric mapping, we compared infarct patterns in stroke patients with and without depression.

Results: Twenty-seven percent (15/55 patients) met criteria for depression at follow-up. Mean infarct volume was 19 ± 53 ml and National Institute of Health Stroke Scale (NIHSS) at Time 1 (within 12 days of stroke) was 4 ± 4, indicating a sample of mild strokes. No voxels or clusters were significant after a multiple comparison correction was applied ($p > 0.05$). Examination of infarct maps showed that there was minimal overlap of infarct location between patients, thus invalidating the voxel comparison analysis.

Conclusions: This study provided inconclusive evidence for the association between infarcts in a specific region and post-stroke depression.

Strengths and limitations of this study:

- This prospective study is the first lesion location study in post-stroke depression to use voxel based analysis. It demonstrates the challenges in using this method of analysis for this cohort and discusses ways of addressing these issues in future research.

- Limitations include that the study provided inconclusive evidence for the association between infarcts in a specific region and post-stroke depression. Additionally, infarct volumes were small, precluding further analysis and suggested that we had unintentionally recruited patients with mild strokes.

Introduction

Post-stroke depression has been described to affect more than 30% of patients with stroke. It has been associated with increased mortality [1-3], cognitive impairment [1], greater functional impairments [4], poorer rehabilitation outcomes [2,3] and reduced health related quality of life [5]. An understanding of patients at risk of post-stroke depression would help guide preventive interventions. To date there is consensus that stroke severity, cognitive impairment, physical disability and handicap correlate with post-stroke depression [6]. The postulate for a neurobiological basis of post-stroke depression was based on observed behavioural changes in rats following focal cortical lesions, and concurrent change in catecholamine levels [7]. Human studies later suggested that depression was more likely after stroke affecting the left hemisphere or frontal lobe [8]. This idea of lesion location impacting on post-stroke depression is an attractive one given the finding of lesion location causing neurological deficit post-stroke [9]. However, the role of lesion location in post-stroke depression remains a point of controversy due to conflicting results [6, 10-11], which could be related to methodological differences between studies.

Modern studies of lesion location use brain imaging analysis tools to characterise ensembles of voxels representing the network of regions involved [9]. However, earlier studies and those assessed in review papers focussed on coarse analyses differentiating left from right hemisphere stroke or anterior versus posterior lesion locations, and their resultant relationship with depression. In light of the improved sensitivity to regional abnormalities afforded by voxel based analysis, the aim of this study was to examine the role of lesion location in post-stroke depression. It was hypothesised that there would be a relationship between lesion location and post-

stroke depression. In the process of performing this analysis we encountered several issues with voxel based analysis for depression in stroke patients.

Materials & methods

Participants

Participants were patients who presented to Monash Medical Centre and Dandenong Hospital with a first cerebral infarction or haemorrhage (*N*=71) in Melbourne, Australia between May 2009 and September 2010. In total, 717 patients were diagnosed with ischaemic stroke and 247 patients with intracerebral haemorrhage during this time frame. Participants were included if they were aged 18-85 years, proficient in English (i.e., capable of completing the assessment materials), and eligible for magnetic resonance imaging (MRI). Participants were excluded if they had a compounding diagnosis (major depressive disorder at the time of admission, a neurodegenerative disease, epilepsy, or an imminently life-threatening comorbid illness), had a subarachnoid or subdural haemhorrage, if a second episode of stroke occurred before follow-up, and/or they were deemed incapable of participation due to incapacity (serious impairment of consciousness or language). The language component of the National Institute of Health Stroke Scale (NIHSS) and the Multilingual Aphasia Examination's (MAE) Token Test (Form A), a 22-item test of oral language comprehension [12], were used to complement clinical judgment in cases with language disturbance. Ethics approval was received from Southern Health and Monash University Human Research Ethics Committees. All participants provided written informed consent.

Test administration and procedure

MRI scans were performed as part of clinical care. Cognitive functioning, stroke severity, physical disability and handicap and demographic information were acquired at Time 1 (typically within 10 days of stroke). Depression was assessed at Time 2 (one month since stroke).

Measures

Cognitive functioning was assessed using the ACE-R [13]. The NIHSS was used to determine stroke severity [14]. The Modified Rankin Scale (MRS) was used to measure both physical disability and handicap [15,16]. The scale ranges from 0-6 from "No symptoms at all", to "Death". The Hospital Anxiety and Depression Scale (HADS) has been used routinely within stroke to screen for symptoms of depression [17]. Those with a cut-off score of 11 on the HADS were further assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.), a semi-structured clinical interview, to confirm a clinical diagnosis of Mood disorder Due to Stroke (CVA) with Major-Depressive Like Episode or with Depressive Features in accordance with DSM-IV inclusion criteria [18,19], abbreviated as 'major' and 'minor' depression below. The M.I.N.I. was administered by a provisional psychologist. This procedure was used to optimise sensitivity, as a cut-off score of 11 on the HADS has been found to have a sensitivity of 86.8 for detecting major and minor depression, and a specificity of 69.9 [20]. The M.I.N.I displays high validity and reliability in relation to the Structured Clinical Interview for DSM, Patient Edition (SCID-P), and the Composite International Diagnostic Interview (CIDI). The M.I.N.I. can be administered in a shorter period of time than the aforementioned tools [18]. A history

of depression was documented if noted in the medical file or reported during the clinical interview.

Image acquisition

MRI scans were performed on a 1.5 Tesla superconducting imaging system (General Electric Medical Systems, Milwaukee, WI) with echo-planar imaging capabilities. T2 images were acquired using thickness 6mm/1.7 mm, matrix 256 x 256, and TR/TE/ETL 2 000/102/12. Diffusion-weighted imaging (DWI) was performed with 6/1.7 mm thickness, matrix 128 x 256, field of view 230 mm, and TR/TE 10,000/102. Diffusion gradient values of 0 s/mm^2 and 1,000 s/mm^2 were applied in 3 directions. Isotropic ADC maps were calculated on a voxel by voxel basis. The 3-D time of flight MRA was performed using TR/TE 38/6.9, 25^0 flip angle, thickness 1.4 mm, slab thickness 60 mm, matrix 256 X 224, field of view 180 mm.

Registration and segmentation

Alignment of corresponding anatomical structures in images (prior to segmentation) from different subjects was achieved by linear registration to a standard brain template comprising images from 152 subjects placed into the stereotaxic coordinate space (MNI template available at http://www.bic.mni.mcgill.ca/software/). Infarcts were manually segmented on the native T_2-weighted images using interactive *Display,* mouse driven software and standardised intensity windows. The transformation matrix was used to convert native segmented images into standard stereotaxic space.

t statistics

A parametric voxel based analysis (SPM; Wellcome Trust Centre for Neuroimaging, London, England) was used to produce statistical parametric maps. Images were spatially smoothed with a Gaussian kernel of 12 mm. This analysis used the two-sample *t* test in SPM5 to compare the distribution of the means of infarcts of patients with and without depression. A spatial mask of the sum of all infarcted regions in this sample (based on images before they were spatially smoothed) was applied so that the voxel analysis was constrained to this area. A false discovery rate (FDR) was used to correct for multiple comparisons, as the *t* statistic is applied to many voxels within the images. The FDR controls the expected proportion of false-positives among the voxels that have exceeded a certain threshold on the raw *t* statistics map [21]. The FDR was set at 0.05 so that among the significant voxels above the *t* threshold, 5% would be considered false-positive. To assess the validity of the *t*-statistics images, an average map of the infarcts was generated. This process allows determination if the analysis contains infarcts which cover most of the brain. Previous investigators have been criticised for performing studies on infarcts belonging to a restricted arterial territory and hence in this study we include infarcts from any arterial territory [22].

Volume and overlap of infarcts

The volume of each infarct was calculated using a voxel counting algorithm. The overlap of infarcts amongst patients was manually examined to aid interpretation of results. The maximum overlap of regions of infarction between (i) all patients was seven; (ii) depressed patients was two; and (iii) patients without depression was seven (see Figures 1 and 2). A mask was used to determine the volume of infarcts in the anterior and posterior regions of the left and right hemispheres.

Results

Clinical Characteristics

Of the 71 participants, 55 (31 males) completed all aspects of the study including an MRI scan. Ten of the 71 patients withdrew or were lost to follow-up, five patients did not undergo a clinical MRI scan and one was excluded following a second episode of stroke. The clinical characteristics of participants are summarised in Table 1. The mean age was 62.9 years (*SD* = 13.6). Eighty percent (*n* = 44) of patients had ischaemic strokes. Twelve patients (22%) had a personal history of depression. The mean NIHSS at Time 1 was 4 ± 4, representing minor strokes. Acute and follow-up assessments were administered within an average of 6 ± 3 days (range 1-12) and 33 ± 8 (range 25-74) days of stroke respectively. MRI scans were performed within an average of 20.8 ± 23.7 days of stroke (0-85 days). Overall, 27.3% of patients experienced depression (*n* = 15), either major (*n* = 9; 16.4%), or minor (*n* = 6; 10.9%). The mean total HADS score was 10 ± 7 (0-29). Three patients (6%) were taking antidepressant medication during the course of the study.

Table 1. Clinical characteristics of participants, (N = 55)

Characteristic	
Mean age ± *SD* (yrs)	63 (*14*)
Range	29-85
Sex, *n* (%)	
Male	31 (56)
Female	24 (44)
Type of stroke, *n* (%)[1]	
Ischaemic	47 (86)
Haemorrhagic	6 (11)
Laterality of stroke, *n* (%)[2]	
Left	29 (53)
Right	20 (36)
Bilateral	5 (9)
Modified Rankin at Time 1[3], *n* (%)	
0-2 (no symptoms-slight disability)	31 (57)
3-5 (moderate-severe disability)	23 (43)
Mean NIHSS at Time 1 ± *SD*	4 ± 4
Range	0-21
Mean ACE-R at Time 1 ± *SD*	78 ± 16
Range	18-99
Mean infarct volume ± *SD* ml	19 ± 53
Range	0-350*
English first language, *n* (%)	40 (73)
Personal history of depression, *n* (%)	12 (22)
Family history of depression, *n* (%)	5 (9)
Antidepressants during study, *n* (%)	3 (6)
Depression at Time 2, *n* (%)	15 (27)

*0 volumes represent scans with no visible infarcts despite clinical diagnosis of stroke.
[1]Two cases of missing data; [2,3]One case of missing data.

Image analysis

The mean infarct volume was 19.4 ± 53.2 ml (0-349.8 ml). The mean volume of haemorrhagic lesions was 44.7 ± 103.9 (0.12-349.83 ml). Stroke occurred in the left hemisphere in twenty nine (52.7%) patients, right hemisphere in 20 patients (36.4%). It was present in both hemispheres in 5 patients (9.1%). The mean volume of infarct in the left hemisphere was 6.2 ± 15.6 ml and the right hemisphere was 38.0 ± 83.2 ml (p = 0.001). The mean volume of infarct in the left anterior region was 4.8 ± 7.7 ml and the right anterior region was 46.9 ± 91.4 ml (p=0.06). The mean volume of

infarct in the left posterior region was 16.2 ± 27.2 compared to 17.6 ± 19.8 ml for the right posterior region (p>0.05). Modified Rankin Scale scores greater than 2 were associated with larger lesion volumes (p = 0.02) and there was a large and medium correlation respectively between NIHSS scores acutely and at one month and lesion volumes (p < 0.05).

The average map of infarcts is displayed in Figure 1 and showed that infarcts occurred predominantly around the internal capsule and striatocapsular region. Infarct extent was greater on the right. The infarct pattern of the depressed group versus the group without depression was significant at the uncorrected level (p < 0.01, see Figure 2). No voxels or clusters were significant after the FDR correction was applied (p > 0.05). Additionally, there was no relationship between left anterior strokes and depression (p > 0.05). Infarct location of stroke by group is displayed in Table 2.

Table 2. Frequency of depressed and non-depressed patients by infarct location identified on MRI scans.

Infarct location	Group	
	Depressed	Not depressed
Left hemisphere, *n* (%)	7 (13)	20 (36)
Left anterior, *n* (%)	4 (7)	13 (24)
Left posterior, *n* (%)	3 (5)	7 (13)
Right hemisphere, *n* (%)	5 (9)	15 (27)
Right anterior, *n* (%)	4 (7)	11 (20)
Right posterior, *n* (%)	1 (2)	3 (5)
Extended across the anterior and posterior cortex, *n* (%)	0	1 (2)
Bilateral, *n* (%)	1 (2)	2 (4)
No infarct on MRI scan	2 (4)	2 (4)

Note. 6 (11%) of infarct locations displayed above differ from values displayed in Table 1 which relate to hemispheric location documented in patients' medical records.

When potential confounders including sex, a history of depression, cognitive functioning (ACE-R) and physical disability and handicap were analysed for inclusion in the image analysis, sex was the only variable significantly related to mood (p<0.0.5). When the infarct analysis was repeated with gender as a covariate, infarct location was not significantly related to depression after a FDR correction was applied (p>0.05). Additionally, when the infarct analysis was repeated excluding cases with no identifiable lesions on their MRI scan, infarct location was not significantly related to depression after a FDR correction was applied (p>0.05). An independent samples t-test indicated no significant difference in lesion volume between groups with and without depression (p>0.05).

Discussion

Based on the results of this study, the contribution of lesion location to the aetiology of post-stroke depression remains inconclusive. In the planning of this study, we had followed the suggestions of previous investigators with regards to including stroke from all arterial territories but in doing so had unintentionally created challenges for ourselves [22]. This study highlights the challenge in conducting voxel based analysis for lesion location studies in post-stroke depression. These issues related primarily to the use of strict inclusion and exclusion criterion, principally, the exclusion of patients with severe dysphasia and those patients who were likely to require institutionalised care. This action posed major challenges for voxel based analysis which required the presence of regions which overlap with each other. Below we discus how these results compare with prior studies, the theoretical implications, the issues affecting our results and propose methods to overcome these shortcomings in future studies of post-stroke depression.

Literature review

The current findings differ from prior studies, many of which have proposed that lesions to the left frontal cortex and basal ganglia are related to the onset of post-stroke depression, and proximity of the lesion to the frontal pole is associated with severity of depression [8,23-27]. More recently, MRI studies have supplemented earlier CT studies, providing further support for a relationship between lesions to the basal ganglia and PSD [28]. Other studies, however, have reported no significant relationship between lesion location and depression, with inconsistent findings attributed to methodological differences including timing of assessment [23,29]. Prior studies have defined lesion location based on whether lesions fall within a particular a

priori defined region of the brain [8]. Hence, whilst the results were less precise than voxel based morphology, overlap of precise lesion location was not required. However, in the current study when the occurrence of depression was compared in patients with anterior and posterior strokes in left and right hemispheres, no relationship was found.

Methodological considerations

i. Image analysis

When analysing the findings of voxel based analysis, one is often drawn to the significant results. A more useful approach is to examine the average map of all infarcts (Figure 1) to ensure there are no regions without infarcts. In our case, the map showed a predilection of larger infarcts in the right hemisphere compared to the left. This visual analysis paralleled our finding with the infarct volume between the hemispheres. These findings preclude any further voxel based analysis.

ii. Inclusion and exclusion criterion

In our patients the infarct volumes were small as was the NIHSS score. This suggested that we had unintentionally recruited patients with mild strokes. This has occurred because of the concern that assessment of depression was unreliable in patients with severe dysphasia. The second problem occurred because patients with larger strokes had impaired alertness and awareness and were not able to provide informed consent; in this study we did not used carer consent as is often done in the initial stage of acute stroke trials. As was the case with our study, the results of prior works were likely biased due to the same pitfall of excluding patients with severe dysphasia.

iii. Sample size

One approach is to significantly increase the sample size to allow the chance of overlapping regions of infarct. However, a 3-fold increase in sample size would only result in an overlap of 6 scans. Hence, it is probable that the selection of 'minor' strokes is significantly contributing to this methodological issue. A larger sample size would not resolve this issue unless the inclusion and exclusion criteria are changed to prevent exclusion of aphasic and severe stroke patients.

Strategies for recruitment may include assessment of patients in the sub-acute rather than the acute phase of stroke (Time 1). This may allow for some degree of neurological recovery, especially among patients with severe strokes, to increase the chance of recruitment of these patients. Alternatively, a non-verbal assessment of depression could be administered, such as the observer-rated Stroke Aphasic Depression Quesionnaire-10 [30] or the Aphasia Depression Rating Scale [31], however, there is currently limited information regarding the psychometric properties of these tools which implies a validation study is necessary as a first step. Finally, restricting inclusion to patients with infarcts within an a priori defined anatomical region would increase overlap of infarcts, although this method has received criticism [32]. Restricting arterial territory has previously lead to adequate overlap and significant results using voxel based analyses [33].

Future directions

Despite the abovementioned challenges encountered with neuroimaging within this patient group, further research is warranted. A greater understanding of the lesion characteristics associated with post-stroke depression could lead to advances in

diagnosis, preventive interventions and treatment. It is clear that post-stroke depression has an unfavourable influence on a range of outcomes; hence there is an important role for interventions. For preventive strategies to be implemented effectively, it is important to identify patients at greatest risk and to intervene, ideally within the acute post-stroke period.

Voxel based analysis could be used in future studies of comparable sample size if inclusion criteria was restricted to an a priori defined homogenous subgroup of patients. This would allow hypothesis testing of the role of particular anatomical locations in post-stroke depression such as the basal ganglia. However, voxel based analysis has limitations, as other potentially relevant infarct locations would not be detected using this approach. Future research should also take into account the influence of pre-existing lesions given the evidence to suggest that cumulative pre-existing lesions may be more important than the location of a single infarct [34].

The high prevalence of depression found within this sample despite no particular significant lesion location related to depression points to the benefit of analysing networks of neural structures implicated in depression, rather than limiting the focus to the significance of lesions to one or two structures. An alternative method of analysis such as partial least squares regression might therefore be more appropriate as this technique would allow the involvement of networks of neural structures to be explored [33]. However, partial least squares regression also relies on overlap of infarcted areas across MRI scans, a condition that was not met in the current dataset. Further overlap of infarcts across stands could potentially be acquired if a non-verbal measure of depression was used to allow for the inclusion of patients with more severe strokes.

Conclusions

In summary, the results of this study do not provide evidence that infarcts to a particular neuroanatomical region contributes to post-stroke depression, however, results should be interpreted with caution due to methodological limitations. Future studies could overcome the methodological issues encountered during our study by assessing patients within the sub-acute rather than the acute post-stroke period, using an observer rated scale of depression rather than measures that require language comprehension abilities, or including patients with infarcts within an a priori defined anatomical region. Alternatively, an analysis of lesions to neurochemical networks implicated in depression could shed light on the debate.

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Disclosure

None

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Contributorship Statement

Sophia Gozzi designed the study, recruited patients, collected and analysed data, drafted and revised the paper. Thanh Phan assisted with the study design, monitored data collection, segmented the infarcts on the MRI scans, assisted with image analysis and critically reviewed the paper. Amanda Wood assisted with the study design, monitored data collection, assisted with image analysis and critically reviewed the paper. Jian Chen assisted with image analysis and critically reviewed the paper. Krishnarao Vaddadi assisted with the study design and critically reviewed the paper. Imogen Rehm, Kitty Wong and May Chong assisted with patient recruitment and data collection

Data Sharing Statement

No additional data available.

Legends to figures

Figure 1: Average map of infarcts for all patients in stereotaxic coordinate space from z = -20 to z = 20 (from left to right).

Figure 2: Average map of infarcts for the depressed (blue) and not depressed (yellow) groups in stereotaxic coordinate space from z = -20 to z = 20 (from left to right).

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Imaging predictors of post-stroke depression: Methodological factors in voxel based analysis

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Results: Twenty-seven percent (15/55 patients) met criteria for depression at follow-up. Mean infarct volume was 19 ± 53 ml and National Institute of Health Stroke Scale (NIHSS) at Time 1 (within 12 days of stroke) was 4 ± 4, indicating a sample of mild strokes. No voxels or clusters were significant after a multiple comparison correction was applied ($p > 0.05$). Examination of infarct maps showed that there was minimal overlap of infarct location between patients, thus invalidating the voxel comparison analysis.

Conclusions: This study provided inconclusive evidence for the association between infarcts in a specific region and post-stroke depression.

Strengths and limitations of this study:

- This prospective study is the first lesion location study in post-stroke depression to use voxel based analysis. It demonstrates the challenges in using this method of analysis for this cohort and discusses ways of addressing these issues in future research.
- Limitations include that the study provided inconclusive evidence for the association between infarcts in a specific region and post-stroke depression. Additionally, infarct volumes were small, precluding further analysis and suggested that we had unintentionally recruited patients with mild strokes.

Introduction

Post-stroke depression~~, i.e., affective disorders following stroke,~~ has been described to affect more than 30% of patients with stroke. It has been associated with increased mortality [1-3], cognitive impairment [1], greater functional impairments [4], poorer rehabilitation outcomes [2,3] and reduced health related quality of life [5]. An understanding of patients at risk of post-stroke depression would help guide preventive interventions. To date there is consensus that stroke severity, cognitive impairment, physical disability and handicap correlate with post-stroke depression [6]. The postulate for a neurobiological basis of post-stroke depression was based on observed behavioural changes in rats following focal cortical lesions, and concurrent change in catecholamine levels [7~~6~~]. Human studies later suggested that depression was more likely after stroke affecting the left hemisphere or frontal lobe [8~~7~~]. This idea of lesion location impacting on post-stroke depression is an attractive one given the finding of lesion location causing neurological deficit post-stroke [9~~8~~]. However, the role of lesion location in post-stroke depression remains a point of controversy due to conflicting results [6, 10~~9~~-11], which could be related to methodological differences between studies.

Modern studies of lesion location use brain imaging analysis tools to characterise ensembles of voxels representing the network of regions involved [9~~8~~]. However, earlier studies and those assessed in review papers focussed on coarse analyses differentiating left from right hemisphere stroke or anterior versus posterior lesion locations, and their resultant relationship with depression. In light of the improved sensitivity to regional abnormalities afforded by voxel based analysis, the aim of this study was to examine the role of lesion location in post-stroke depression. It was

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hypothesised that there would be a relationship between lesion location and post-stroke depression. In the process of performing this analysis we encountered several issues with voxel based analysis for depression in stroke patients.

Materials & methods

Participants

Participants were patients who presented to Monash Medical Centre and Dandenong Hospital with a first cerebral infarction or haemorrhage (*N*=71) in Melbourne, Australia between May 2009 and September 2010. In total, 717 patients were diagnosed with ischaemic stroke and 247 patients with intracerebral haemorrhage during this time frame. Participants were included if they were aged 18-85 years, proficient in English (i.e., capable of completing the assessment materials), and eligible for magnetic resonance imaging (MRI). Participants were excluded if they had a compounding diagnosis (major depressive disorder at the time of admission, a neurodegenerative disease, epilepsy, or an imminently life-threatening comorbid illness), had a subarachnoid or subdural haemhorrage, if a second episode of stroke occurred before follow-up, and/or they were deemed incapable of participation due to incapacity (serious impairment of consciousness or language). The language component of the National Institute of Health Stroke Scale (NIHSS) and the Multilingual Aphasia Examination's (MAE) Token Test (Form A), a 22-item test of oral language comprehension [12], were used to complement clinical judgment in cases with language disturbance. Ethics approval was received from Southern Health and Monash University Human Research Ethics Committees. All participants provided written informed consent.

Test administration and procedure

MRI scans were performed as part of clinical care. Cognitive functioning, stroke severity, physical disability and handicap and demographic information were acquired at Time 1 (typically within 10 days of stroke). Depression was assessed at Time 2 (one month since stroke).

Measures

Cognitive functioning was assessed using the ACE-R [13]. The NIHSS was used to determine stroke severity [14]. The Modified Rankin Scale (MRS) was used to measure both physical disability and handicap [15,16]. The scale ranges from 0-6 from "No symptoms at all", to "Death". The Hospital Anxiety and Depression Scale (HADS) has been used routinely within stroke to screen for symptoms of depression [17]. Those with a cut-off score of 11 on the HADS were further assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.), a semi-structured clinical interview, to confirm a clinical diagnosis of Mood disorder Due to Stroke (CVA) with Major-Depressive Like Episode or with Depressive Features~~major or minor depression~~ in accordance with DSM-IV inclusion criteria [18,19], abbreviated as 'major' and 'minor' depression below. The M.I.N.I. was administered by a provisional psychologist. This procedure was used to optimise sensitivity, as a cut-off score of 11 on the HADS has been found to have a sensitivity of 86.8 for detecting major and minor depression, and a specificity of 69.9 [20]. The M.I.N.I displays high validity and reliability in relation to the Structured Clinical Interview for DSM, Patient Edition (SCID-P), and the Composite International Diagnostic Interview (CIDI). The M.I.N.I. can be administered in a shorter period of time than the

aforementioned tools [18]. A history of depression was documented if noted in the medical file or reported during the clinical interview.

Image acquisition

MRI scans were performed on a 1.5 Tesla superconducting imaging system (General Electric Medical Systems, Milwaukee, WI) with echo-planar imaging capabilities. T2 images were acquired using thickness 6mm/1.7 mm, matrix 256 x 256, and TR/TE/ETL 2 000/102/12. Diffusion-weighted imaging (DWI) was performed with 6/1.7 mm thickness, matrix 128 x 256, field of view 230 mm, and TR/TE 10,000/102. Diffusion gradient values of 0 s/mm^2 and 1,000 s/mm^2 were applied in 3 directions. Isotropic ADC maps were calculated on a voxel by voxel basis. The 3-D time of flight MRA was performed using TR/TE 38/6.9, 25^0 flip angle, thickness 1.4 mm, slab thickness 60 mm, matrix 256 X 224, field of view 180 mm.

Registration and segmentation

Alignment of corresponding anatomical structures in images (prior to segmentation) from different subjects was achieved by linear registration to a standard brain template comprising images from 152 subjects placed into the stereotaxic coordinate space (MNI template available at http://www.bic.mni.mcgill.ca/software/). Infarcts were manually segmented on the native T_2-weighted images using interactive *Display,* mouse driven software and standardised intensity windows. The transformation matrix was used to convert native segmented images into standard stereotaxic space.

t statistics

A parametric voxel based analysis (SPM; Wellcome Trust Centre for Neuroimaging, London, England) was used to produce statistical parametric maps. Images were spatially smoothed with a Gaussian kernel of 12 mm. This analysis used the two-sample *t* test in SPM5 to compare the distribution of the means of infarcts of patients with and without depression. A spatial mask of the sum of all infarcted regions in this sample (based on images before they were spatially smoothed) was applied so that the voxel analysis was constrained to this area. A false discovery rate (FDR) was used to correct for multiple comparisons, as the *t* statistic is applied to many voxels within the images. The FDR controls the expected proportion of false-positives among the voxels that have exceeded a certain threshold on the raw *t* statistics map [21]. The FDR was set at 0.05 so that among the significant voxels above the *t* threshold, 5% would be considered false-positive. To assess the validity of the *t*-statistics images, an average map of the infarcts was generated. This process allows determination if the analysis contains infarcts which cover most of the brain. Previous investigators have been criticised for performing studies on infarcts belonging to a restricted arterial territory and hence in this study we include infarcts from any arterial territory [22].

Volume and overlap of infarcts

The volume of each infarct was calculated using a voxel counting algorithm. The overlap of infarcts amongst patients was manually examined to aid interpretation of results. The maximum overlap of regions of infarction between (i) all patients was seven; (ii) depressed patients was two; and (iii) patients without depression was seven (see Figures 1 and 2). A mask was used to determine the volume of infarcts in the anterior and posterior regions of the left and right hemispheres.

Results

Clinical Characteristics

Of the 71 participants, 55 (31 males) completed all aspects of the study including an MRI scan. Ten of the 71 patients withdrew or were lost to follow-up, five patients did not undergo a clinical MRI scan and ~~and~~ one was excluded following a second episode of stroke. The clinical characteristics of participants are summarised in Table 1. The mean age was 62.9 years (*SD* = 13.6). Eighty percent (*n* = 44) of patients had ischaemic strokes. Twelve patients (22%) had a personal history of depression. The mean NIHSS at Time 1 was 4 ± 4, representing minor strokes. Acute and follow-up assessments were administered within an average of 6 ± 3 days (range 1-12) and 33 ± 8 (range 25-74) days of stroke respectively. MRI scans were performed within an average of 20.8 ± 23.7 days of stroke (0-85 days). Overall, 27.3% of patients experienced depression (*n* = 15), either major (*n* = 9; 16.4%), or minor (*n* = 6; 10.9%). The mean total HADS score was 10 ± 7 (0-29). Three patients (6%) were taking antidepressant medication during the course of the study.

Table 1. Clinical characteristics of participants, ($N = 55$)

Characteristic	
Mean age ± *SD* (yrs)	63 (*14*)
Range	29-85
Sex, *n* (%)	
Male	31 (56)
Female	24 (44)
Type of stroke[1], *n* (%)[1]	
Ischaemic	47 (86)
Haemorrhagic	6 (11)
Laterality of stroke[2], *n* (%)[2]	
Left	29 (53)
Right	20 (36)
Bilateral	5 (9)
Modified Rankin at Time 1[3], *n* (%)	
0-2 (no symptoms-slight disability)	31 (57)
3-5 (moderate-severe disability)	23 (43)
Mean NIHSS at Time 1 ± *SD*	4 ± 4
Range	0-21
Mean ACE-R at Time 1 ± *SD*	78 ± 16
Range	18-99
Mean infarct volume ± *SD* ml	19 ± 53
Range	0-350*
English first language, *n* (%)	40 (73)
Personal history of depression, *n* (%)	12 (22)
Family history of depression, *n* (%)	5 (9)
Antidepressants during study, *n* (%)	3 (6)
Depression at Time 2, *n* (%)	15 (27)

*0 volumes represent scans with no visible infarcts despite clinical diagnosis of stroke.
[1]Two cases of missing data; [2,3]One case of missing data.

Image analysis

The mean infarct volume was 19.4 ± 53.2 ml (0-349.8 ml). The mean volume of haemorrhagic lesions was 44.7 ± 103.9 (0.12-349.83 ml). Stroke occurred in the left hemisphere in twenty nine (52.7%) patients, right hemisphere in 20 patients (36.4%). It was present in both hemispheres in 5 patients (9.1%). The mean volume of infarct in the left hemisphere was 6.2 ± 15.6 ml and the right hemisphere was 38.0 ± 83.2 ml ($p = 0.001$). The mean volume of infarct in the left anterior region was 4.8 ± 7.7 ml and the right anterior region was 46.9 ± 91.4 ml ($p=0.06$). The mean volume of

infarct in the left posterior region was 16.2 ± 27.2 compared to 17.6 ± 19.8 ml for the right posterior region (p>0.05). Modified Rankin Scale scores greater than 2 were associated with larger lesion volumes (p = 0.02) and there was a large and medium correlation respectively between NIHSS scores acutely and at one month and lesion volumes (p < 0.05).

The average map of infarcts is displayed in Figure 1 and showed that infarcts occurred predominantly around the internal capsule and striatocapsular region. Infarct extent was greater on the right. The infarct pattern of the depressed group versus the group without depression was significant at the uncorrected level (p < 0.01, see Figure 2). No voxels or clusters were significant after the FDR correction was applied (p > 0.05). Additionally, there was no relationship between left anterior strokes and depression (p > 0.05). Infarct location of stroke by group is displayed in Table 2.

Table 2. Frequency of depressed and non-depressed patients by infarct location identified on MRI scans.

Infarct location	Group	
	Depressed	Not depressed
Left hemisphere, *n* (%)	7 (13)	20 (36)
Left anterior, *n* (%)	4 (7)	13 (24)
Left posterior, *n* (%)	3 (5)	7 (13)
Right hemisphere, *n* (%)	5 (9)	15 (27)
Right anterior, *n* (%)	4 (7)	11 (20)
Right posterior, *n* (%)	1 (2)	3 (5)
Extended across the anterior and posterior cortex, *n* (%)	0	1 (2)
Bilateral, *n* (%)	1 (2)	2 (4)
No infarct on MRI scan	2 (4)	2 (4)~~3 (5)~~

Note. 6 (11%) of infarct locations displayed above differ from values displayed in Table 1 which relate to hemispheric location documented in patients' medical records.

When potential confounders including sex, a history of depression, cognitive functioning (ACE-R) and physical disability and handicap were analysed for inclusion in the image analysis, sex was the only variable significantly related to mood (p<0.0.5). When the infarct analysis was repeated with gender as a covariate, infarct location was not significantly related to depression after a FDR correction was applied (p>0.05). Additionally, when the infarct analysis was repeated excluding cases with no identifiable lesions on their MRI scan, infarct location was not significantly related to depression after a FDR correction was applied (p>0.05). An independent samples t-test indicated no significant difference in lesion volume between groups with and without depression (p>0.05).

Discussion

Based on the results of this study, the contribution of lesion location to the aetiology of post-stroke depression remains inconclusive. In the planning of this study, we had followed the suggestions of previous investigators with regards to including stroke from all arterial territories but in doing so had unintentionally created challenges for ourselves [22]. This study highlights the challenge in conducting voxel based analysis for lesion location studies in post-stroke depression. These issues related primarily to the use of strict inclusion and exclusion criterion, principally, the exclusion of patients with severe dysphasia and those patients who were likely to require institutionalised care. This action posed major challenges for voxel based analysis which required the presence of regions which overlap with each other. Below we discus how these results compare with prior studies, the theoretical implications, the issues affecting our results and propose methods to overcome these shortcomings in future studies of post-stroke depression.

Literature review

The current findings differ from prior studies, many of which have proposed that lesions to the left frontal cortex and basal ganglia are related to the onset of post-stroke depression, and proximity of the lesion to the frontal pole is associated with severity of depression [8~~7~~,23-27]. More recently, MRI studies have supplemented earlier CT studies, providing further support for a relationship between lesions to the basal ganglia and PSD [28]. Other studies, however, have reported no significant relationship between lesion location and depression, with inconsistent findings attributed to methodological differences including timing of assessment [23,29]. Prior studies have defined lesion location based on whether lesions fall within a particular a

priori defined region of the brain [87]. Hence, whilst the results were less precise than voxel based morphology, overlap of precise lesion location was not required. However, in the current study when the occurrence of depression was compared in patients with anterior and posterior strokes in left and right hemispheres, no relationship was found.

Methodological considerations

i. Image analysis

When analysing the findings of voxel based analysis, one is often drawn to the significant results. A more useful approach is to examine the average map of all infarcts (Figure 1) to ensure there are no regions without infarcts. In our case, the map showed a predilection of larger infarcts in the right hemisphere compared to the left. This visual analysis paralleled our finding with the infarct volume between the hemispheres. These findings preclude any further voxel based analysis.

ii. Inclusion and exclusion criterion

In our patients the infarct volumes were small as was the NIHSS score. This suggested that we had unintentionally recruited patients with mild strokes. This has occurred because of the concern that assessment of depression was unreliable in patients with severe dysphasia. The second problem occurred because patients with larger strokes had impaired alertness and awareness and were not able to provide informed consent; in this study we did not used carer consent as is often done in the initial stage of acute stroke trials. As was the case with our study, the results of prior works were likely biased due to the same pitfall of excluding patients with severe dysphasia.

iii. Sample size

One approach is to significantly increase the sample size to allow the chance of overlapping regions of infarct. However, a 3-fold increase in sample size would only result in an overlap of 6 scans. Hence, it is probable that the selection of 'minor' strokes is significantly contributing to this methodological issue. A larger sample size would not resolve this issue unless the inclusion and exclusion criteria are changed to prevent exclusion of aphasic and severe stroke patients.

Strategies for recruitment may include assessment of patients in the sub-acute rather than the acute phase of stroke (Time 1). This may allow for some degree of neurological recovery, especially among patients with severe strokes, to increase the chance of recruitment of these patients. Alternatively, a non-verbal assessment of depression could be administered, such as the observer-rated Stroke Aphasic Depression Quesionnaire-10 [30] or the Aphasia Depression Rating Scale [31], however, there is currently limited information regarding the psychometric properties of these tools which implies a validation study is necessary as a first step. Finally, restricting inclusion to patients with infarcts within an a priori defined anatomical region would increase overlap of infarcts, although this method has received criticism [32]. Restricting arterial territory has previously lead to adequate overlap and significant results using voxel based analyses [33].

Future directions

Despite the abovementioned challenges encountered with neuroimaging within this patient group, further research is warranted. A greater understanding of the lesion characteristics associated with post-stroke depression could lead to advances in

diagnosis, preventive interventions and treatment. It is clear that post-stroke depression has an unfavourable influence on a range of outcomes; hence there is an important role for interventions. For preventive strategies to be implemented effectively, it is important to identify patients at greatest risk and to intervene, ideally within the acute post-stroke period.

Voxel based analysis could be used in future studies of comparable sample size if inclusion criteria was restricted to an a priori defined homogenous subgroup of patients. This would allow hypothesis testing of the role of particular anatomical locations in post-stroke depression such as the basal ganglia. However, voxel based analysis has limitations, as other potentially relevant infarct locations would not be detected using this approach. Future research should also take into account the influence of pre-existing lesions given the evidence to suggest that cumulative pre-existing lesions may be more important than the location of a single infarct [34].

The high prevalence of depression found within this sample despite no particular significant lesion location related to depression points to the benefit of analysing networks of neural structures implicated in depression, rather than limiting the focus to the significance of lesions to one or two structures. An alternative method of analysis such as partial least squares regression might therefore be more appropriate as this technique would allow the involvement of networks of neural structures to be explored [33]. However, partial least squares regression also relies on overlap of infarcted areas across MRI scans, a condition that was not met in the current dataset. Further overlap of infarcts across stands could potentially be acquired if a non-verbal measure of depression was used to allow for the inclusion of patients with more severe strokes.

~~Additionally, the high prevalence of depression found within this sample despite no particular significant lesion location related to depression points to the benefit of analysing networks of neural structures implicated in depression, rather than limiting the focus to the significance of lesions to one or two structures. This approach could involve an a priori hypothesis regarding lesions restricting particular neurochemical pathways and associated structures or an alternative type of analysis that explores the significance of neural networks to the outcome of interest, such as partial least squares regression. Voxel based analysis could therefore be used in future studies of comparable sample size if inclusion criteria was restricted to an a priori defined homogenous subgroup of patients. This would allow hypothesis testing of the role of particular anatomical locations in post-stroke depression such as the basal ganglia. However other potentially relevant infarct locations would not be detected using this approach. An alternative method of analysis such as partial least squares regression might therefore be more appropriate as this technique would allow the involvement of networks of neural structures to be explored (Phan et al., 2010). However, partial least squares regression also requires the presence of infarcts in regions which overlap across images and would therefore only be appropriate if a non-verbal measure of depression was used to allow for the inclusion of patients with more severe strokes. Preliminary investigations showed that neither voxel based analysis nor partial least squares regression were appropriate in this study due to the nature of the data.~~

Conclusions

In summary, the results of this study do not provide evidence that infarcts to a particular neuroanatomical region contributes to post-stroke depression, however, results should be interpreted with caution due to methodological limitations. Future studies could overcome the methodological issues encountered during our study by

assessing patients within the sub-acute rather than the acute post-stroke period, using an observer rated scale of depression rather than measures that require language comprehension abilities, or including patients with infarcts within an a priori defined anatomical region. Alternatively, an analysis of lesions to neurochemical networks implicated in depression could shed light on the debate.

Disclosure

None

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Legends to figures

Figure 1: Average map of infarcts for all patients in stereotaxic coordinate space from z = -20 to z = 20 (from left to right).

Figure 2: Average map of infarcts for the depressed (blue) and not depressed (yellow) groups in stereotaxic coordinate space from z = -20 to z = 20 (from left to right).

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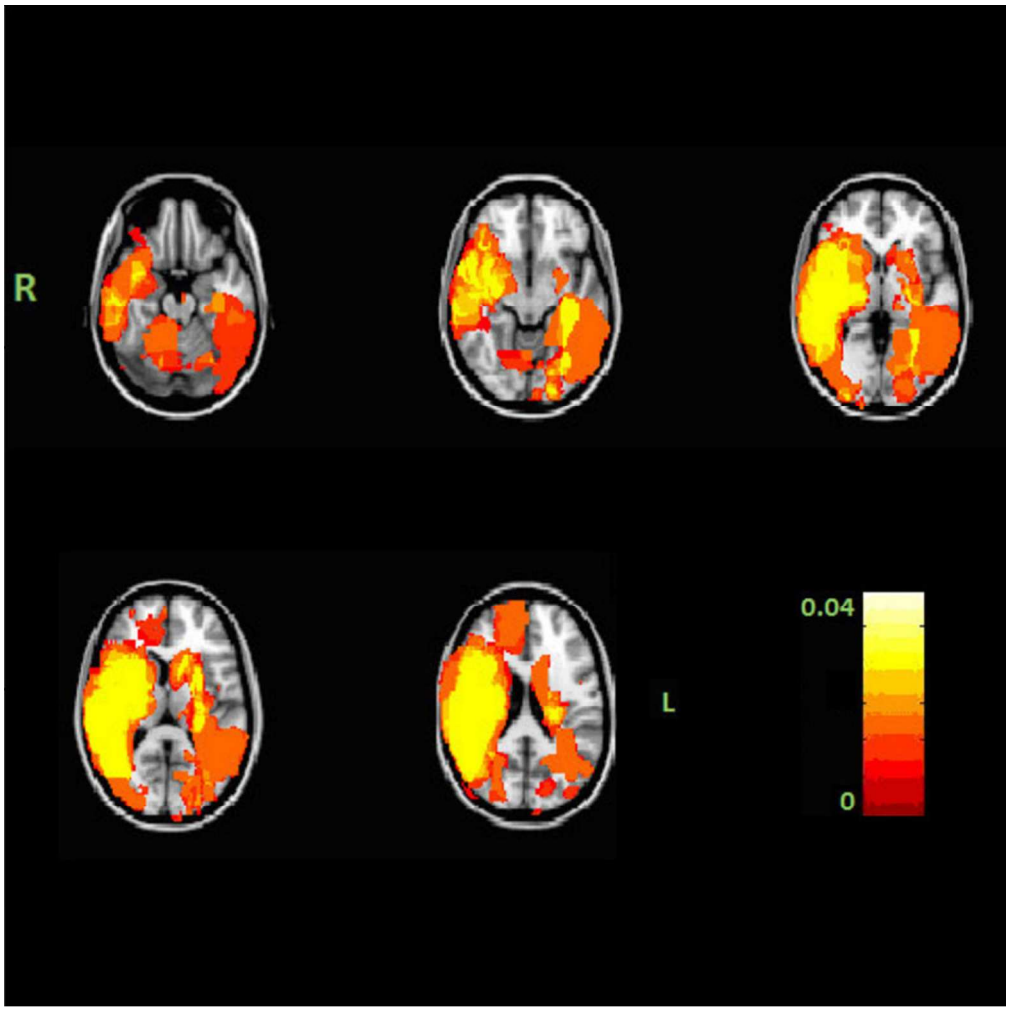

Figure 1: Average map of infarcts for all patients in stereotaxic coordinate space from z = -20 to z = 20 (from left to right).
90x90mm (300 x 300 DPI)

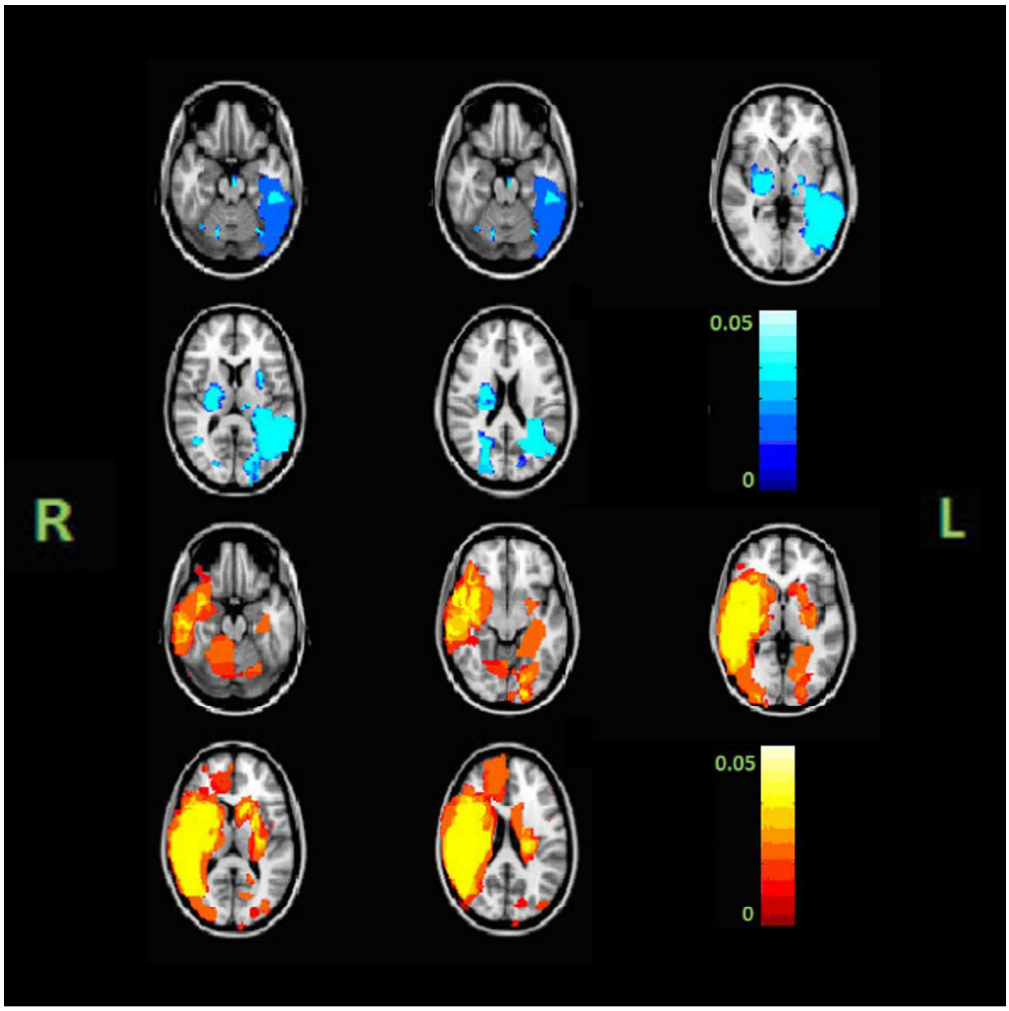

Figure 2: Average map of infarcts for the depressed (blue) and not depressed (yellow) groups in stereotaxic coordinate space from z = -20 to z = 20 (from left to right).
90x90mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y
Methods			
Study design	4	Present key elements of study design early in the paper	Y
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Y
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Y
Bias	9	Describe any efforts to address potential sources of bias	Y
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y
		(*b*) Describe any methods used to examine subgroups and interactions	Y
		(*c*) Explain how missing data were addressed	Y
		(*d*) If applicable, explain how loss to follow-up was addressed	Y
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y
		(b) Give reasons for non-participation at each stage	Y
		(c) Consider use of a flow diagram	Y
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y
		(b) Indicate number of participants with missing data for each variable of interest	Y
		(c) Summarise follow-up time (eg, average and total amount)	Y
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	N/A

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Y
Discussion			
Key results	18	Summarise key results with reference to study objectives	Y
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.